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(54) Composition for soluble films with a new hydrolyzed polysaccharide

(57) The invention is concerned with film-forming compositions containing hydrolysates of the exopolysaccharide YAS34 for the use in pharmaceutical, veterinary, food, cosmetic or other products like films for wrapping food, aspics or jellies, preferably for predosed formulations like soft or hard capsules.

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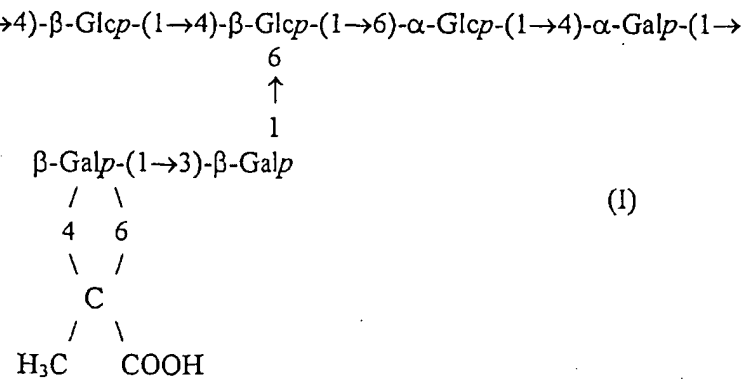
Description

[0001] The invention is concerned with film-forming compositions containing hydrolysates of the new exopolysaccharide YAS34 for the use in pharmaceutical, veterinary, food, cosmetic or other products like films for wrapping food, aspics or jellies, preferably for predosed formulations like soft or hard capsules.

[0002] A second embodiment of the invention is the use of the inventive composition for the manufacture of hard capsules by conventional dip molding process as normally used in the production of conventional hard gelatin capsules.

[0003] The new exopolysaccharide (EPS) is a bacterial polysaccharide "YAS34", produced by the soil bacteria Rhizobium Leguminasorum and developed under the trade name Soligel by ARD (Pomade, France).

[0004] The repeating unit of YAS34 consisting of one glucuronic acid (GlcA), six neutral sugars of which 3 are galactoses (Gal) and 3 are glucoses (Glc), one pyruvate group and 1.6 acetate groups in average per unit (not located yet) is shown in scheme I:



(I)

[0005] The production of YAS34 and the use as thickening agent, gelling agent, suspension agent, water retention agent, soil aggregation agent, texturing agent and seed coating agent is disclosed in WO98/35993.

[0006] YAS34 has a thermal reversible gelling ability and excellent properties for forming films with sufficient mechanical characteristics for the manufacturing of capsules, especially hard capsules. A disadvantage of the YAS34-films however is the poor water solubility at 37°C. It takes 50 minutes to dissolve a film of 100 µm thickness whereas a conventional gelatin film will be dissolved in only 2 minutes. A further disadvantage of YAS34 is its very high viscosity resulting from the very high molecular weight of the polysaccharide. But high viscosity and gelling ability result in the impossibility of forming films by casting or dip moulding, especially for hard capsules from solutions having an EPS concentration above 10 %. Especially for the production of hard capsules high solid contents of the film forming aqueous solution are required. Low solid content will result in non-uniform film forming, long drying time and low productivity.

[0007] Surprisingly we have found that the disadvantages can be overcome by hydrolysis of YAS34, which reduces efficiently the molecular weight and the viscosity of the aqueous solution viscosity. Furthermore the solubility of the polysaccharide film is significantly improved. Though some alterations of the mechanical properties have been observed, they remain at an acceptable level for the requirements of hard capsules.

[0008] The original polysaccharide YAS34 has a molecular weight of 1,400,000. An aqueous solution of 5 % by weight gelatinizes at 60°C and the the working temperature has to be above 60°C for capsule manufacturing. If the concentration is increased to 10%, the working temperature has to be increased above 80°C. Such conditions are quite inconvenient and energy consuming for an industrial manufacturing process.

[0009] The hydrolysis of YAS34 under acid conditions is very efficient as demonstrated in experiments. Under the conditions given in example 1, within one hour, the molecular weight of the polysaccharide is reduced below 200,000 which can be used for the preparation of film-forming aqueous solutions with a content above 20 %. Such solutions have acceptable viscosity even at room temperature. For this reason the molecular weight of the hydrolyzed YAS34 is preferably between 500,000 and 10,000 which allows the preparation of film-forming solutions in the range from 10 to 50% by weight.

[0010] Within the preferred Mw range the mechanical properties of the film remain quite acceptable even for hard capsule production.

[0011] Conventional hard capsules are produced from gelatin by a dip moulding process. This process is based on the setting ability of hot gelatin solution by cooling. On a totally automatic industrial hard gelatin capsule machine, mould pins are dipped into hot gelatin solution, the pins are removed from the solution, inverted, the gelatin solution (gel) remaining on the pins dried, stripped off the capsule shells and finally cap and body of the capsules cut and pre-

joined. The immediate setting of the gelatin solution on the mould pins after dipping is the key step in the process. Otherwise, the gelatin solution would flow down to form capsules with non-uniform wall thickness and unacceptable properties.

[0012] However the aqueous solution of the hydrolyzed polysaccharide YAS34 does not gelatinize at room temperature and does not have the necessary setting ability for hard capsule manufacturing by the described conventional dip moulding process. Surprisingly we have found that the addition of an additional setting agent to the aqueous solution or to the film-forming composition allows the adjustment and optimization of the setting ability of the solution to achieve uniform shell thickness of hard capsules.

[0013] Preferred setting agents for the inventive film-forming compositions or the aqueous solutions thereof are carrageenan, gellan gum, pectin, agarose, gelatin, xanthan with locust bean gum, xanthan with konjac, or unhydrolyzed YAS34. The preferred content of the setting agent in the solid film composition is 0.5 % to 15 % by weight. In the aqueous solution the setting agent is in the range of 0.05 % to 5 % by weight. Optionally the gelling agents are combined with mono or divalent cations like Calcium Ca^{++} or Mg^{++}, e.g. water-soluble salts therof, preferably in the aqueous solution in an amount of 0.01 to 3 % or in the solid film composition in an amount of 0.1 to 5% by weight.

[0014] Aqueous solutions of the inventive film-forming composition containing hydrolyzed YAS34 and a setting agent and the films derived therefrom have following advantages:

- High solid content which improves significantly the feasibility of different manufacturing processes.
- Sufficient setting ability for hard capsule production by conventional dip moulding process.
- High solubility of the films, suitable for predosed formulations such as hard capsules, soft capsules, tablet coating and ingredient packaging.
- Acceptable mechanical properties of the films for hard capsules allowing filling and blistering operations.

[0015] The inventive composition may contain in a further aspect additional plasticizer, especially for soft film formulations such as soft capsules.

[0016] The inventive composition may contain in a further aspect additional coloring agents or flavoring agents.

[0017] The hard capsules of the invention may be used as containers for providing unit dosage forms, e.g. for agrochemicals, seeds, herbs, foodstuffs, dyestuffs, pharmaceuticals, flavouring agents and the like.

Example 1

Hydrolysis of the native polysaccharide YAS34

[0018] 15 g of YAS34 are dissolved in distilled water at 52°C to form a solution containing 1.5 % by weight to which 1000 ml 2M HCl are added under stirring. The mixture is incubated at 52°C for A 1 hour and in a second batch B for 1.5 hours. After the given incubation time the solution is cooled to room temperature and neutralized to pH 7. The hydrolysates are precipitated with a water/ethanol (50/50 v/v) and washed 4 times with ethanol.

[0019] Molecular weights and viscosity of YAS34 and hydrolysates are shonw in Table 1:

Table 1

	Mw average	Viscosity (cps)
YAS34	1,400,000	5% at 50°C gelatinized 5% at 60°C gelatinized
Hydrolysate A	123,000	20% at 50°C 650
Hydrolysate B	45,000	27% at 50°C 300

[0020] The results in Table 1 demonstrate that hydrolysis under mild conditions efficiently reduces molecular weight and viscosity and the hydrolysates are well suitable for the preparation of aqueous solutions with acceptable viscosity and solid content for the manufacturing of hard or soft capsules.

Example 2

Polysaccharide films

[0021]

a) 50 g YAS34 are dissolved in distilled water at 90°C to form a solution of 10 % by weight. After debubbling the solution was stabilized at 80°C. Films with a thickness about 100 µm were prepared by casting the solution on glass plates and drying at 22°C / 50 % RH over night.

b) 50 g hydrolysate B (Mw ≈ 45,000) are dissolved in distilled water at 60°C to form a solution of 27 %. After debubbling, the solution was stabilized at 50°C. Films with a thickness about 100 µm were prepared by casting the solution on glass plates and drying at 22°C / 50 % RH over night.

[0022] The dissolution times of the films shown in Table 2 are determined according to UPS XXII dissolution test method conditions (at 37°C, in demineralyzed water).

Table 2

	YAS34	Hydrolysate B	Gelatin
Dissolution (min)	51	1.2	2.2

[0023] The mechanical properties of the films shown in Table 3 are determined by tensile tests with an Instron machine with films equilibrated by 50 % RH at 22°C before test.

Table 3

	YAS34	Hydrolysate B
Young's modulus (MPa)	2400	2880
Strength (MPa)	59	55
Elongation at break (%)	19	9

[0024] The result of the tests demonstrate that hydrolysate B has a significantly higher dissolution rate than YAS34. The dissolution is even better than gelatin. The tensile strenght of the hydrolysate is reduced when compared with YAS34 but the mechanical properties remain very acceptable not only for soft but even for hard capsule manufacturing.

Example 3

Hard capsules from hydrolysate B

[0025] 54 g hydrolysate B and 4 g of YAS34 are dissolved in distilled water at 70°C to 200 g of a solution containing 27 % hydrolysate B and 2 % YAS34 by weight. After debubbling the solution was stabilized at 60°C.

[0026] The solution thus prepared was then poured into a dipping dish of a single pin pilot machine of conventional hard gelatin capsule production equipment. Hard capsules of size 1 were produced under similar conditions to hard gelatin capsule production. The produced hard capsules have similar dimensions to the conventional gelatin hard capsules.

[0027] The produced hard capsules were evaluated by disintegration tests according to USPXXIII at 37°C in demineralized water:

First leak	1.4 minute
Total disintegration	9.5 minutes

Claims

1. Film-forming composition containing hydrolyzed exopolysaccharide YAS34.

2. Film-forming composition according to claim 1, wherein the EPS YAS34 is hydrolyzed to an average molecular weight range from 500,000 to 10,000.

3. Film composition according to claim 2, wherein the hydrolyzed YAS34 has an average molecular weight of 45,000.

4. Film composition, according to claims 1 to 3 containing an additional setting agent for processing purpose.

5. Film composition according to claim 4, wherein the setting agent is selected from carrageenan, gellan gum, pectin, agorose, gelatin, xanthan with locust bean gum, xanthan with konjac, or native EPS YAS34.

6. Film composition according to claims 4 or 5, wherein the setting agent is contained in an amount of 0.5 to 15 % by weight.

7. Film composition according to claims 4 to 6, wherein the setting agent is combined with salts of mono or divalent cations.

8. Film composition according to claim 7, wherein the cation salt is contained in an amount of 0.01 to 5 % by weight of the whole composition.

9. Film composition according to claims 1 to 8 containing additionally coloring agents, flavoring agents and/or plasticizers.

10. Container produced from the film-forming composition according to claims 1 to 9 for unit dosage forms of agrochemicals, seeds, herbs, foodstuffs, pharmaceuticals or flavoring agents.

11. An aqueous solution of the film-forming composition according to claims 1 to 9 for the manufacturing of soft and hard capsules.

12. The aqueous solution according to claim 11 containing hydrolyzed EPS YAS34 in an amount of 10 to 50%, preferably 15 to 40% by weight of the aqueous solution.

13. The aqueous solution according to claims 11 and 12 containing an additional setting agent in an amount of 0.01 to 5%, preferably 0.03 to 3% by weight of the aqueous solution.

14. The aqueous solution according to claims 11 to 13 containing additionally salts of mono or divalent cations in an amount of 0.01 to 3%, preferably 0.01 to 1% by weight of the aqueous solution.

15. Use of the aqueous solution according to claims 11 and 14 for the manufacturing of hard capsules in a dip moulding process.

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EUROPEAN SEARCH REPORT

Application Number
EP 00 40 2437

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
X	AGNÈS VILLAIN-SIMONNET ET AL.: "A new bacterial polysaccharide (YAS34)." INT. J. BIOL. MACROMOL., vol. 27, no. 1, 2000, pages 65-75, XP002159348 Amsterdam * page 69; table 2 *	1,2,11, 12	C08J5/18 A61K9/48 C08L5/00 C12P19/04
X	AGNÈS VILLAIN-SIMONNET ET AL.: "A new bacterial exopolysaccharide (YAS34)" INTERNATIONAL JOURNAL OF BIOLOGICAL MACROMOLECULES, vol. 27, no. 1, 2000, pages 77-87, XP002159349 Amsterdam * page 85 - page 86 *	1-14	
Y	US 4 306 059 A (KOJI YOKOBAYASHI ET AL.) 15 December 1981 (1981-12-15) * examples 1-3,13 *	1-14	
Y	GB 2 223 503 A (AGRICULTURAL & FOOD RESEARCH COUNCIL) 11 April 1990 (1990-04-11) * page 7, paragraph 2 *	1-14	TECHNICAL FIELDS SEARCHED (Int.Cl.7) C08J A61K C08L C12P

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	5 February 2001	Lensen, H

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 00 40 2437

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
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